PATENT SPECIFICATION

818,269

Date of Application and filing Complete Specification: Feb. 4, 1957.

No. 3814/57.

Application made in Germany on Feb. 4, 1956.

Complete Specification Published: Aug. 12, 1959.

Index at acceptance:—Class 2(3), B4(A2:E:K:M).

International Classification:—C07d.

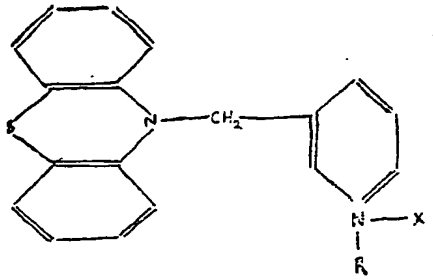
COMPLETE SPECIFICATION

Improvements in or relating to the preparation of Phenthiazine Derivatives

We, CHEMISCHE FABRIK PROMONTA G.M.B.H., a Body Corporate organized under the laws of Germany, of Hammer Landstrasse 162-178, Hamburg 26, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with improvements in or relating to the preparation of phenthiazine derivatives and is more particularly concerned with a process for the production of 10-(N-lower alkylpiperidyl-3¹-methyl)-phenthiazine. By "lower alkyl" we mean alkyl groups containing from one to four carbon atoms.

The value of 10-(N-methylpiperidyl-3¹-methyl)-phenthiazine for therapeutic purposes has been established. We have now found that compounds of this type, that is the above compound and those which only differ therefrom in that the nitrogen atom of the piperidyl group is substituted with a lower alkyl group other than a methyl group, can be obtained more advantageously and in better yields than hitherto, by alkylating phenthiazine with (pyridyl-3)-methyl chloride or bromide, or an acid addition salt thereof, in the presence of an inert organic solvent and an alkali metal condensation agent, quaternizing the 10-(pyridyl-3¹-methyl)-phenthiazine obtained with a lower alkyl halide to obtain a lower alkyl pyridinium halide derivative of the formula



wherein R is a lower alkyl group and X is halogen, and then catalytically hydrogenating the lower alkyl pyridinium halide derivative to obtain 10-(N-lower alkyl-piperidyl-3¹-methyl)-phenthiazine.

Organic compounds containing sulphur cannot be hydrogenated with conventional hydrogenation catalysts of the non-precious metal series such as nickel, cobalt and copper chromite as such catalysts are inactivated by the sulphur. Catalysts of the precious metal series such as platinum and palladium can be used but have been found uneconomical both on account of their costliness and as a result of their partial inactivation. More recently, however, metal sulphide hydrogenation catalysts have been discovered which are resistant to inactivation by sulphur present in heterocyclic combination and it is such catalysts which should be employed in the present process. The most important of such catalysts are the sulphides of metals of Group VIa and VIII of the periodic system, in particular molybdenum sulphide, nickel sulphide and cobalt sulphide, (see E. H. M. Badger *et al, Proc. Roy. Soc.* (*L*), Ser. A.197 (1949), pages 184-194, Chem. Zentrallblatt 1950, II, 870).

According to the present invention, therefore, there is provided a process for the preparation of 10-(N-lower alkyl piperidyl-3¹-methyl)-phenthiazines which comprises alkylating phenthazine with (pyridyl-3)-methyl chloride or bromide or an acid addition salt thereof in the presence of an inert organic solvent and an alkali metal condensation agent, quaternizing the 10-pyridyl-3¹-methyl)phenthiazine obtained with a lower alkyl halide containing not more than 4 carbon atoms, and then catalytically hydrogenating the lower alkyl pyridinium halide derivative thus obtained in the presence of a metal sulphide hydrogenation catalyst resistant to inactivation by sulphur present in heterocyclic combination to yield 10-(N-lower alkyl piperidyl-3¹-methyl)-phenthiazine.

[*Price 3s. 6d.*]

Suitable inert organic solvents for the alkylation stage are, for example, benzene, toluene, xylene and tetralin (Registered Trade Mark), while suitable condensation agents for this stage are, for example the alkali metals themselves or their hydrides, amides or oxides, such as lithium hydride, sodamide and sodium oxide.

Preferred hydrogenation catalysts for use in the final stage of the process are, as indicated above, molybdenum sulphide, cobalt sulphide and nickel sulphide.

In order that the invention may be more fully understood, the following examples are given by way of illustration only:—

STAGE I: ALKYLATION

EXAMPLE 1

10 - (Pyridyl - 3^1 - methyl) - phenthiazine.

155 g of phenthiazine, 7 g of lithium hydride (in a further similar example, 36 g of Sodamide) and 600 ccs of dry xylene, were placed in a 2-litre three-necked flask provided with a stirrer, reflux condenser, dropping funnel and thermometer, and the mixture was boiled under reflux while stirring until the formation of hydrogen (or ammonia) ceases. A solution of 78 g of (pyridyl-3)-methyl chloride in 500 ccs of xylene (which had been obtained immediately beforehand from a concentrated aqueous solution of 105 g of (pyridyl-3)-methyl chloride-hydrochloride by alkalization and salting out into xylene with potash, this process being accompanied by adequate cooling, was then added dropwise over a period of 2 hours. After this addition was complete, the reaction was continued for a further hour. The reaction mixture was then allowed to cool, the surplus lithium hydride (or sodamide) being decomposed with a small quantity of alcohol and the reaction product being decomposed with water. The xylene solution was washed with a copious supply of water, stirred with hydrochloric acid and left to stand; 10-(pyridyl-3^1-methyl)-phenthiazine hydrochloride crystallized out and was filtered off. Additional quantities of hydrochloride could be obtained by concentrating the aqueous solution still further. The hydrochloride was recrystallized, after treatment in solution with active carbon, from dilute hydrochloric acid to give light yellow needles with m.p. 115—117°C. It was possible to obtain the free base from the salt by dissolving the latter in water and adding caustic soda or ammonia. 165 g (= 93% of the theoretical yield) of 10-(pyridyl-3^1-methyl)-phenthiazine (m.p. 103—104°C) were obtained after recrystallization from dilute alcohol. The sulphate (from water) melts at 173°C.

EXAMPLE 2

In a 2-litre flask provided with stirrer, reflux condenser, filling device and thermometer, were placed 155 g of phenthiazine, 95 g of sodium oxide and 1 litre of dry tetralin (Registered Trade Mark), and the mixture was heated to 150—165°C. Over a period of 3 hours, 100 g of finely-powdered (pyridyl-3)-methyl chloride-hydrochloride was added, in very small amounts at a time. Owing to the considerable excess of sodium oxide, the halogen base was not liberated until it reached the reaction flask. The mixture was heated for a further hour and then allowed to cool, after which the reaction product was decomposed with water. After the solution had been washed with a copious quantity of water, the mixture was worked up as indicated in Example 1.

This process yielded 139 g (= 81% of the theoretical yield) of crystallized 10-(pyridyl-3^1-methyl)-phenthiazine (m.p. 104—105°C).

STAGE II: QUATERNIZATION

The quaternary salts of 10-(pyridyl-3^1-methyl)-phenthiazine were obtained by reacting the base with a lower alkyl halide in an autoclave or a bomb tube, using a solvent such as alcohol, acetone, ethyl acetate or benzene, at temperatures between 30 and 120°C.

EXAMPLE 3.

Phenthiazine - 10 - methyl - (1^1 - methyl-pyridinium - 3^1)chloride

From 100 g of 10-(pyridyl-3^1-methyl)-phenthiazine and 20 g of methyl chloride in acetone at 80—100°C. Yield quantitative. Slightly yellow, coarse needles from alcohol/acetone (m.p. 136—137°C.).

EXAMPLE 4

Phenthiazine - 10 - methyl - (1^1 - methyl-pyridinium - 3^1) - bromide

From 100 g of 10-(pyridyl-3^1-methyl)-phenthiazine and 45 g of methyl bromide in benzene or acetone at room temperature. (Can be obtained more rapidly in an autoclave at 50—70°C). Yield quantitative. Slightly yellow crystals from water m.p. of hydrate; 75—78°C. (m.p. of anhydrous compound: 210—211°).

EXAMPLE 5

Phenthiazine - 10 - methyl - (1^1 - ethyl-pyridinium - 3^1)bromide

From 100 g of 10-(pyridyl-3^1-methyl)-phenthiazine and 50 g of ethyl bromide in acetone or benzene at 80—100°C. Yield: 95% of theoretical yield. Slightly yellow crystals from alcohol/acetic ester. (m.p. 215—216°C).

EXAMPLE 6

Phenthiazine - 10 - methyl - (1^1 - n - propylpyridinium - 3^1)bromide

From 100 g of 10-(pyridyl-3-methyl)-phenthiazine and 55 g of *n*-propyl bromide in acetone at 100°C. Yield: 88% of theoretical yield. Slightly yellow crystals from alcohol. (m.p. 209—211°C).

EXAMPLE 7

Phenthiazine - 10 - methyl - (1^1 - *iso*-propylpyridinium - 3^1 -)bromide

From 100 g of 10-(pyridyl-3-methyl)-phenthiazine and 60 g of *iso*propyl bromide in ethyl acetate at 120—150°C. Yield 56% of

theoretical yield. Slightly yellow crystals from acetone (m.p. 95—97°C).

EXAMPLE 8

Phenthiazine - 10 - methyl - (1^1 - n - butyl-pyridinium - 3^1)bromide

From 100 g of 10-(pyridyl-3^1-methyl)-phenthiazine and 60 g of *n*-butyl bromide in alcohol at 100—120°C. Yield 72% of theoretical yield. Slightly yellow crystals from alcohol. (m.p. 188—189°C.).

STAGE III: HYDROGENATION OF (N-LOWER-ALKYL - PIPERIDYL - 3^1)METHYL-PHENTHIAZINES.

EXAMPLE 9

10 - (N - methyl - piperidyl - 3)-methyl-phenthiazine

A high-pressure stirring autoclave was fed with 100 g of phenthiazine-10-methyl-(1^1-methylpyridinium-3^1) bromide and 40 g of a hydrogenation catalyst consisting of molybdenum sulphide in 700 ccs of 50% methanol, after which hydrogen sulphide was introduced and 150—200 atm. abs. of hydrogen added under pressure. Then the autoclave is put into operation. The absorption of hydrogen commences at 120°C and is found to terminate when 165°C is reached. The cooled contents of the autoclave are filtered off, the crystal mass and the catalyst boiled out 3 times with water and washed with hot water, the clear aqueous methanolic filtrates concentrated and freed of methanol and left to stand in the refrigerator. The 10-(N-methylpiperidyl - 3^1 - methyl)-phenthiazine hydrobromide, which is very difficult to dissolve in cold water, crystallized out. After the mother liquors have been worked up, and dissolved and recrystallized from water, there is a hydrobromide yield of 101 g (= 80% of the theoretical yield) with m.p. of 209—211°C. The free bases are obtained from an aqueous solution of the hydrobromide, by alkalination. The 10-(N-methyl-piperidyl - 3^1 - methyl)-phenthiazine is dissolved and recrystallized from light petroleum, and melts at 80—81°C. The resulting hydrochloride (from aqueous isopropanol) has m.p. of 180—182°C when in the form of a monohydrate and m.p. of 230—232°C when in an anhydrous state, while the lactate (from ethyl acetate) has m.p. of 109—110°C and the oxalate (from dilute alcohol) m.p. of 232—233° C.

EXAMPLE 10

10 - (N-ethyl-piperidyl-3^1-methyl)-phenthiazine

A high-pressure stirring autoclave is fed with 100 g of phenthiazine-10-methyl-(1^1-ethyl-pyridinium-3^1) bromide and 50 g of a hydrogenation catalyst consisting of cobalt sulphide in 700 ccs of dilute methanol, after which the air is removed, hydrogen sulphide introduced and 150—200 atm. abs. of hydrogen added under pressure. The hydrogenation commences between 130 and 150°C. and comes to an end at 165°C. The cooled contents of the autoclave are filtered off, the residue washed with hot water and the filtrates further concentrated in a vacuum. The 10-(N-ethyl-piperidyl - 3^1 - methyl)-phenthiazine hydrobromide crystallizes out, and is dissolved and recrystallized from water. There is a yield of 70 g (= 69% of the theoretical yield) of colourless crystals with m.p. of 250—252° C. The resulting hydrochloride (from *iso*-propanol) melts at 231—233°C.

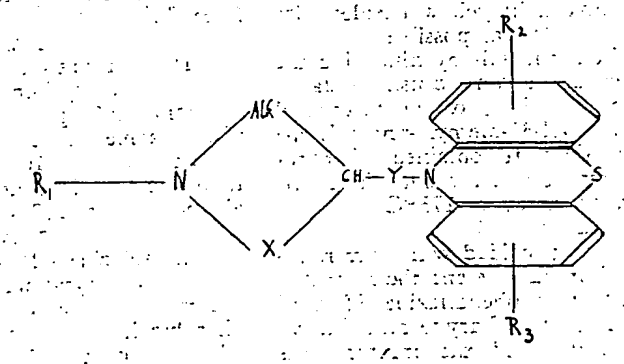
EXAMPLE 11

10 - (N - n - propyl - piperidyl - 3^1 - methyl)-phenthiazine

A high pressure stirring autoclave is fed with 100 g of phenthiazine-10-methyl-(1^1-*n*-propyl - pyridinium - 3^1)bromide and 30 g of a hydrogenation catalyst consisting of molybdenum sulphide in 700 ccs of dilute methanol, after which the air is removed, hydrogen sulphide introduced and 150—200 atm. abs. of hydrogen added under pressure. The hydrogenation takes place at between 130 and 170°C. The cooled hydrogenation solution is filtered off and then worked up as indicated in Example 9.

After recrystallization from water, there is a yield of 73 g (= 72% of the theoretical yield) of 10-(N-*n*-propyl-piperidyl-3^1-methyl)-phenthiazine hydrobromide with m.p. of 211—212°C. The hydrochloride (from *iso*-propanol) thus produced via the oily base melts at 169—170°C.

In our own earlier Patent Specification No. 772,179 we have claimed, as new compounds, phenothiazine derivatives of the general formula:



wherein R_1 is an alkyl radical containing not more than 4 carbon atoms; R_2 and R_3 are hydrogen or ring-attached halogen atoms or alkyl or alkoxy groups; Alk is a branched or unbranched alkylene group containing not more than 3 carbon atoms in a straight chain; and X and Y each represents either a direct linkage or a branched or unbranched alkylene group containing no more than 3 carbon atoms in a straight chain between the adjacent nitrogen atom and CH group.

WHAT WE CLAIM IS:—

1. A process for the preparation of 10-(N-lower alkyl piperidyl-3¹-methyl)-phenthiazines which comprises alkylating phenthiazine with (pyridyl-3)-methyl chloride or bromide or an acid addition salt thereof in the presence of an inert organic solvent and an alkali metal condensation agent, quaternizing the 10-(pyridyl-3¹-methyl)-phenthiazine obtained with a lower alkyl halide containing not more than 4 carbon atoms, and then catalytically hydrogenating the lower alkyl pyridinium halide derivative thus obtained in the presence of a metal sulphide hydrogenation catalyst resistant to inactivation by sulphur present in heterocyclic combination to yield a 10-(N-lower-alkyl piperidyl-3¹-methyl)-phenthiazine.

2. A process as claimed in claim 1 in which the hydrogenation catalyst is a sulphide of a metal of Groups VI A or VIII of the periodic system.

3. A process according to either of the preceding claims in which the hydrogenation catalyst is molybdenum sulphide, cobalt sulphide or nickel sulphide.

4. A process according to any of the preceding claims in which the inert organic solvent present during the alkylation reaction is benzene, toluene, xylene, or tetrahydronaphthalene.

5. A process according to any of the preceding claims in which the alkali metal condensation agent for the alkylation reaction is an alkali metal or a hydride, amide, or oxide of an alkali metal.

6. A process according to claim 5 in which the alkali metal condensation agent is lithium hydride, sodium amide or sodium oxide.

7. A process for the preparation of 10-(N-lower - alkyl piperidyl - 3¹ - methyl) - phenthiazines substantially as herein described with reference to any of the examples.

8. 10-(N-lower alkyl piperidyl-3¹-methyl)-phenthiazines when prepared by a process as claimed in any of the preceding claims.

For the Applicants
SANDERSON & CO.,
26—28 Bedford Row, London, W.C.1.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1959.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.